Cutaneous Necrosis Due to Norepinephrine: * II. Mechanism and Prevention

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The increased use of norepinephrine (Levophed®) during recent years has been accompanied by more frequent reports of cutaneous necrosis resulting from its administration by continuous intravenous infusion. Although these complications have not resulted in serious threat to life, the prolongation of hospitalization and economic loss may be of considerable magnitude by the time a large slough of skin of an extremity has been removed and the defect grafted and healed. In a recent report [7] 61 documented instances of cutaneous necrosis occurring in 50 patients during the period between January 1951 and April 1956 were collected.

The present study is concerned with two separate aspects of this problem: a) The mechanisms involved in the production of cutaneous necrosis by norepinephrine, and b) The efficacy of two adrenergic blocking agents in the prevention of such necrosis.

I. Mechanism of Slough

The ultimate cause of skin necrosis during norepinephrine infusion is considered to be intense and prolonged ischemia of the skin and subcutaneous tissues due to marked constriction of the vessels supplying these tissues. Constriction has been shown to be the uniform response of these vessels to systemically administered epinephrine or norepinephrine.[1, 2, 12, 16, 18] Chambers and Zweifach [6] have shown that this constrictor response is accentuated during hypotension produced by hemorrhage or trauma, an important observation, since hypotension is almost invariably present in the clinical situations in which norepinephrine is used. These facts explain how slough results when a solution of norepinephrine extravasates and infiltrates the subcutaneous layer. They do not explain how a slough results when the vein is securely tied around a plastic catheter. Two main theories have been advanced to explain such a slough. One theory suggests that spasm in the "infusion" vein leads to backflow through its tributaries and results in prolonged venular and arteriolar spasm,[3, 17] and that the reduced venous pressure associated with arterial hypotension may promote backflow due to the hydrostatic pressure of the infusion. The second theory maintains that spasm of the "infusion" vein and its vasa vasorum leads to diffusion of norepinephrine through the vein wall.[8, 15] The relationship of the area of necrosis to the tip of the catheter and the course of the vein favors the latter theory. Only one author [19] has allocated any causal importance to thrombosis of the infusion vein. Many have agreed that inadequate flow through the distally ligated infusion vein is probably of some importance since it prevents sufficient dilution of the drug within the vein.

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Experimental Results

In five dogs the lesser saphenous vein was exposed for about four to five inches by gentle dissection. A polyethylene catheter was inserted one inch into the vein and the vein securely tied around the catheter and distal to it. In no instance did this result in significant spasm of the vein. A mixture of four mg. of norepinephrine in one liter of five per cent dextrose solution was allowed to drip slowly (12 to 18 drops per minute) into the vein. In four of the five dogs intense spasm at the level of the catheter tip developed in ten to 100 seconds. During the next few minutes spasm gradually extended up the entire visible length of the vein. At the same time the tributary veins became spastic at their junctions with the infusion vein. The skin incision was then closed with clips and opened for inspection of the vein every half hour. Within one to three hours the spastic areas showed progressive blanching. The spasm was sufficient to limit the rate of flow of the infusion. If the catheter was injected forcibly by syringe, however, the spastic segment dilated and spasm did not recur. Although the spasm began to disappear spontaneously after four to seven hours, extreme pallor of the vein persisted. On close inspection vasa vasorum were originally visible in the adventitia of the infusion vein. As pallor of the infusion vein developed, these vasa vasorum presumably also became spastic since they could no longer be seen. Only mild blanching of the tissues along the course of the vein was noted in three of the five animals. After six to eight hours the infusion was discontinued and the vein excised for microscopic study. The wounds were sutured, and the dogs given penicillin. No sloughs developed.

Two dogs were handled in an identical manner except that they were first bled rapidly until the blood pressure fell to 50 mm. of mercury. Both of these dogs developed distinct blanching of the tissues adjacent to the infusion vein. This blanching paralleled the infusion vein, rather than the tributary veins. A large necrotic area developed along the skin incision in one of these dogs.

Thrombosis occurred in two of the seven infusions veins but involved only the segment between the vein ligature and the catheter tip.

II. Prevention of Slough

The measures commonly recommended for the prevention of slough have included administration of norepinephrine in the muscular part of the arm, use of a catheter rather than a needle, and passage of long plastic catheters into major veins in the thoracic or abdominal cavities to provide greater dilution of the drug by the increased blood flow.

Hot packs, ice bags, subcutaneous injections of hyaluronidase, or hyaluronidase and procaine have been tried therapeutically without apparent success. A physiologic antagonist of norepinephrine appeared to be the logical choice as a prophylactic agent. Since amino oxidase, which inactivates norepinephrine at the effector cell level,[5, 13, 23] is not available, the adrenergic blocking drugs phentolamine (Regitine®) and tolazoline (Priscoline®) were employed.

Experimental Results

Four dogs were anesthetized with intravenous pentobarbital and the lower legs shaved. Three ml. of a five per cent dextrose solution containing 8 mg. of norepinephrine were injected subcutaneously with a 26-gauge hypodermic needle in the center of the shaved areas, and the injections repeated every 20 minutes for four to six hours. In the sixteen legs so treated, only five developed sloughs.

The experiments were then repeated in a new series of 17 dogs in which rapid bleeding preceded the norepinephrine in-

TABLE I. *Experimental Incidence of Slough Following Repeated Subcutaneous Injections of Norepinephrine*

	Average Minimum Duration of Exposure to Norepinephrine Injections	Number of Legs Injected	Number of Legs Sloughed	Per Cent Sloughed
Normotensive dogs	5 hours	16	5	31
Hypotensive dogs	5⅓ hours	32	28	88

jections. Each of these dogs received 1.5 mg. of heparin per Kg. of body weight and then was bled rapidly until the mean arterial blood pressure fell to 50 mm. of Hg. Norepinephrine injections were then given in each dog's four legs at 20 minute intervals as in the first series without further bleeding or transfusion. Sixteen of the 17 dogs survived. One front leg and one hind leg of each dog were used as controls. A slough resulted in 28 of these 32 control legs (Table I).

The contralateral 32 extremities were used for testing the efficacy of several drugs in the prevention of slough. After 4 to 6 hours of exposure to norepinephrine, during which interval the injected areas became pale, cold and boggy, the ischemic areas were infiltrated with the following prophylactic drug combinations: 1.5 mg. of Regitine® with 75 units of hyaluronidase—8 legs; 1.0 mg. of Regitine® with 75 units of hyaluronidase—4 legs; 1.0 mg. of Regitine® without hyaluronidase—4 legs; 15 mg. of Priscoline®—3 legs; 15 mg. of Priscoline® with 75 units of hyaluronidase—4 legs; 75 units of hyaluronidase alone—5 legs. Each drug or drug combination injected was diluted to 8 ml. with normal saline, the contralateral control leg being infiltrated at the same time with 8 ml. of normal saline. Thus for each treated leg the contralateral leg served as a control, and no treated legs were considered in the results unless the control leg developed a slough. All animals received three daily injections of 300,000 units of penicillin to minimize the possible role of infection in producing sloughs. In four instances norepinephrine injections were continued for two hours after Regitine® was given.

The results of these trials are outlined in Table II. In none of the 16 legs treated with Regitine®, with or without hyaluronidase, did a slough develop in contrast to the 16 control legs, all of which developed sloughs. In none of the 7 legs treated with Priscoline®, with or without hyaluronidase, did a slough develop despite the appearance of slough in each control leg. Hyaluronidase alone not only failed to prevent slough in all five legs, but these sloughs were as large as or larger than those in the control legs.

III. Discussion

The course of events during prolonged continuous intravenous administration of norepinephrine strongly suggests that diffusion of the drug through the severely ischemic vein wall resulted in ischemia of the adjacent tissues. Indirect evidence for this concept is the fact that the ischemia paralleled the entire course of the infusion vein above the tip of the catheter, and the fact that continuous backflow through tributary veins appeared to be prevented by spasm.

The important role of increased sensitivity of the smaller vessels to chemical stimuli in hemorrhagic hypotension is demonstrated by the increase in the incidence of slough after a standard trauma in dogs who were first bled to moderately severe hypotensive levels. Although pentobarbital apparently does increase vasomotor tone

TABLE II. *Results of Preventive Treatment* *

Therapeutic Combinations	Hours Exposure of Each Leg to Norepinephrine	Number of Legs Treated	Number of Instances of Sloughing
Regitine (1.0 mg.) plus hyaluronidase (75 u.)	4	4	0
	6	4	0
Regitine (1.0 mg.) plus hyaluronidase (75 u.)	5	4	0
Regitine (1.0 mg.)	5	4	0
Priscoline (15 mg.) plus hyaluronidase (75 u.)	6	4	0
Priscoline (15 mg.)	6	3	0
Hyaluronidase (75 u.)	5	2	2
	6	3	3

* This series is composed entirely of hypotensive dogs. A slough developed in each of the control legs paired with the above treated legs.

and peripheral resistance in dogs,[22] it is doubtful that it played any significant role in this series of experiments. In any event both control and hypotensive groups received pentobarbital in comparable dosage. One of the possible factors important in the increased incidence of necrosis when intravenous norepinephrine is used in the leg rather than the arm, is that a selectively greater reduction in venous return from the lower extremities probably occurs in hemorrhagic shock.[4]

The transmission of impulses from adrenergic nerve endings to effector cells is mediated by norepinephrine.[9-11] This transmission is blocked by Regitine® in adequate dosage and the block undoubtedly lasts at least several hours.[14] This concept was tested by injecting norepinephrine for two additional hours in four of the Regitine® treated legs and observing that norepinephrine no longer had any noticeable effect. Priscoline® is considerably less potent as an adrenergic blocking agent, but has a direct histamine-like dilating effect.

Microscopic study of specimens taken from the margins of sloughs or impending sloughs from 24 to 120 hours after the experiments revealed no evidence of vascular thrombosis until the third or fourth day when the slough was well established. The high incidence of slough in a group of dogs given large doses of heparin also helps dispel any consideration of thrombosis as a significant etiologic factor.

The effect of infiltrating the boggy, cold pallid legs with Regitine® and hyaluronidase solution was dramatic. Within 15 to 30 minutes the edema began to subside and the skin became pink and warm, the color and warmth exceeding that of areas of skin not involved in the experiment. Although Regitine® alone effectively prevented slough, the addition of hyaluronidase appeared to accelerate the reversal of ischemia. Hyaluronidase alone appeared to have a slightly harmful effect in the few experimental trials, which confirms our one clinical result with it. Although Priscoline® prevented slough in every instance, the benefit was more immediately apparent with Regitine® during the course of the experiments. McGinn and Schluger [20] on the basis of their experiments with rabbits recently recommended clinical trial of Regitine® for prevention of sloughs.

IV. Clinical Aspects

On the basis of these experiments and those of McGinn and Schluger, it seemed advisable that Regitine® and hyaluronidase be tried clinically in the prevention of sloughs due to prolonged infusion of norepinephrine.

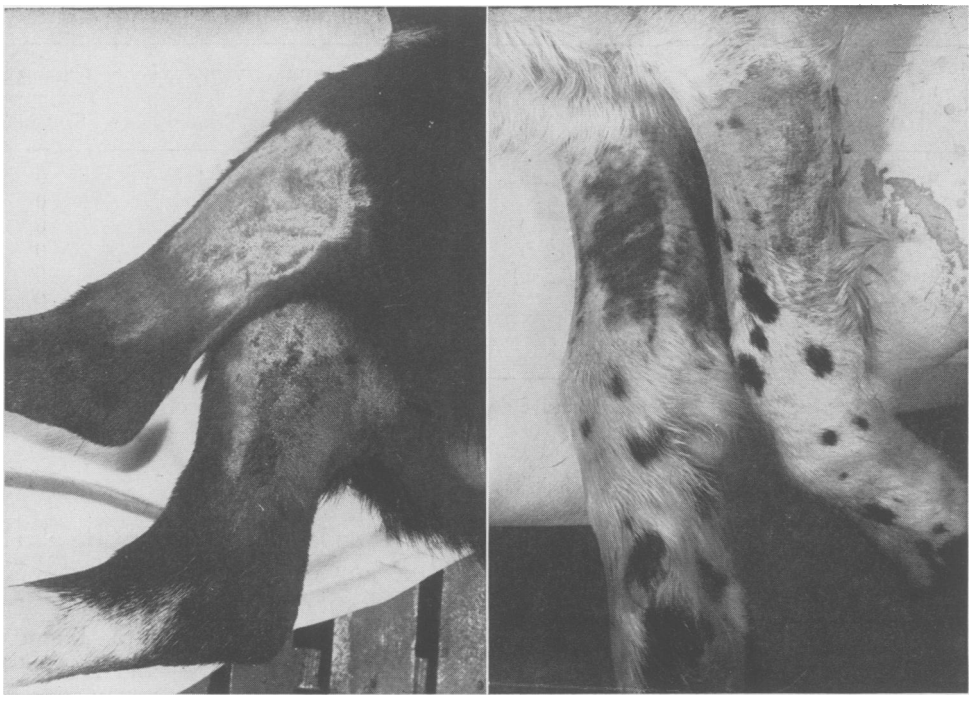

FIG. 1. Upper leg: Infiltrated with 1.0 mgm. Regitine and 75 units hyaluronidase after 5 hours norepinephrine injections. Lower leg: Control.

FIG. 2. Right leg: 1.0 mgm. Regitine after 5 hours exposure to norepinephrine. Left leg: Control.

The infused extremity of any patient receiving norepinephrine should be inspected periodically for areas of pallor and decreased skin temperature. With the development of ischemia the patient frequently complains of pain in the area, and tenderness is usually elicited. Since the duration of the ischemia appears to be the most important factor in determining the eventual outcome, early recognition is essential so that Regitine® infiltration may be begun without delay. At this time 2.5 to 5.0 mg. of Regitine® and 300 units of hyaluronidase in 10 to 30 ml. of saline (the amounts depending on the size of the ischemic area) are injected subcutaneously throughout areas of ischemia.

Thus far this regimen has been employed in 15 patients with no untoward effects. In none of these patients did a slough develop. This clinical experience although favorable is not considered conclusive, since it is not certain that sloughs would have developed had Regitine® not been given.

If it appears that a patient who has developed cutaneous ischemia will need prolonged administration of norepinephrine a high saphenous phlebostomy is performed and a plastic catheter is passed into the iliac vein. This technic consistently avoids ischemia in our experience.

V. Summary

1. The results of this study indicate that factors responsible for the necrosis are either extravasation or marked spasm and ischemia of the infusion vein with diffusion of the drug through its wall. The ischemia is much more severe in the presence of hypotension associated with hemorrhage or trauma due to an increased sensitivity of

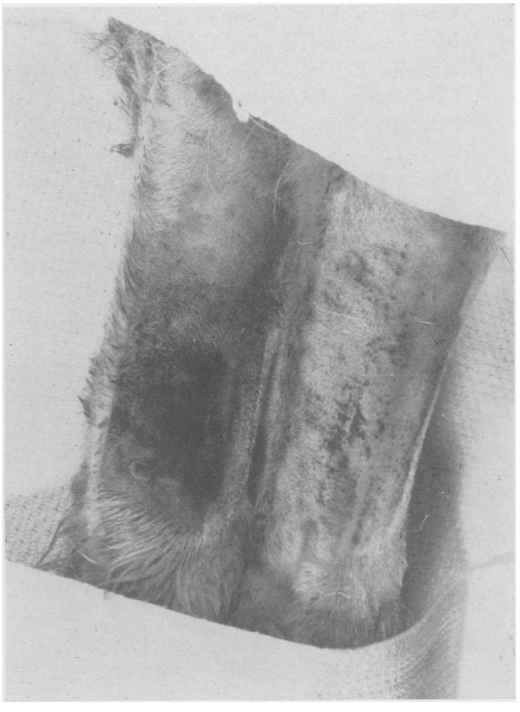

FIG. 3. Right leg: 15 mgm. Priscoline after 6 hours exposure to norepinephrine. Left leg: Control.

the vessels to norepinephrine-induced constriction.

2. A technic which produces slough in 88 per cent of legs injected subcutaneously with norepinephrine has been utilized to study the therapeutic possibilities of three agents in the prevention of such necrosis.

3. When a dog's leg, which has been exposed to norepinephrine in concentration and duration sufficient to produce slough, is infiltrated with 1.0 mg. of Regitine® no slough will result even if the norepinephrine is injected for two additional hours following treatment. The ischemia will be reversed more rapidly if hyaluronidase is added to the solution, whereas hyaluronidase alone has a deleterious effect. Although Priscoline® in 15.0 mg. dosage appears to offer the same protection, its beneficial action is slower and less striking.

4. Clinical trials of a Regitine®-hyaluronidase regimen have thus far been employed successfully in 15 patients with no untoward side effects.

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